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**Parker**

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(54) **MOTOR FIBRE NEUROMODULATION**

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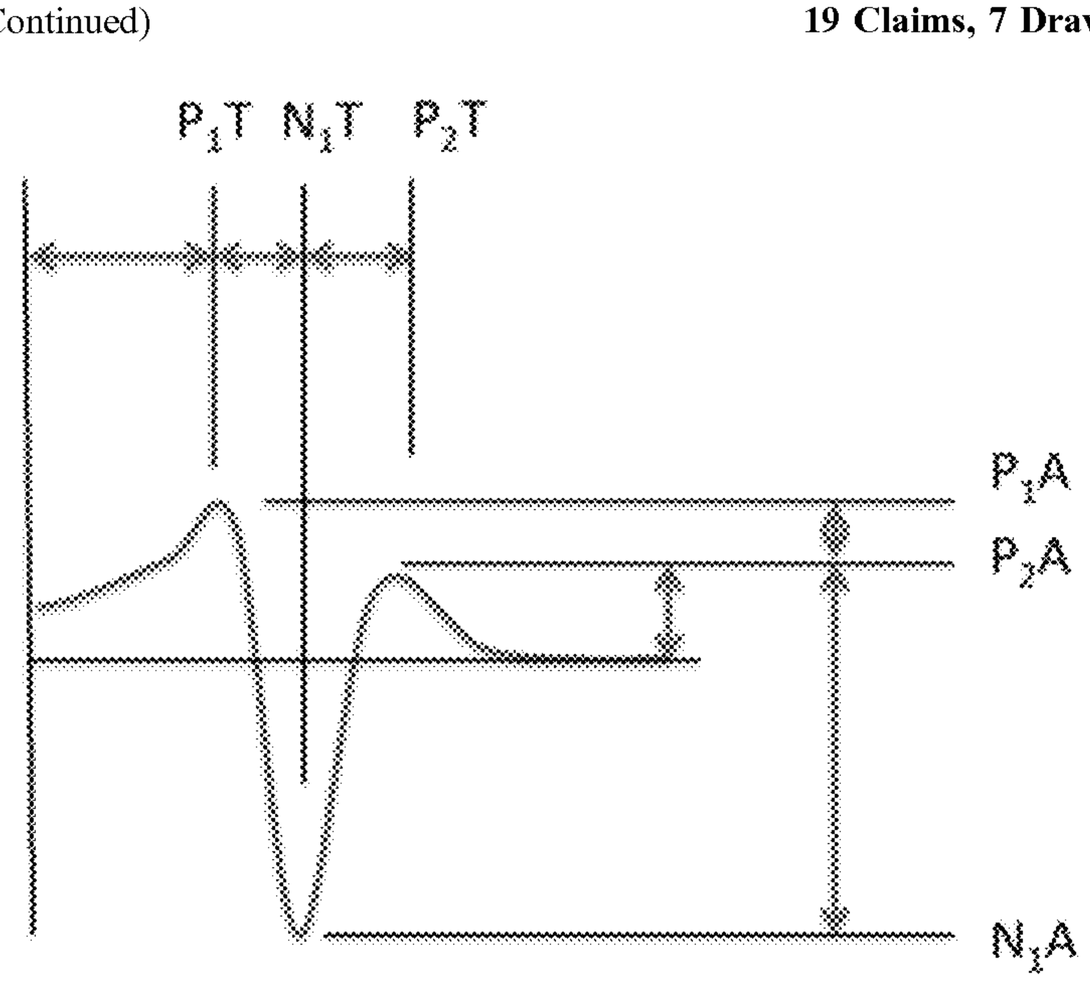
(57) **ABSTRACT**

A motor response of a muscle to neural stimulation is assessed. Electrical stimuli are applied from a first electrode to a selected neural pathway to evoke an efferent neural response. A slow neural response upon the neural pathway evoked by the electrical stimuli is observed. Based on the slow neural response, a motor response of at least one muscle to the stimuli is assessed.

**19 Claims, 7 Drawing Sheets**



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(58) **Field of Classification Search**

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See application file for complete search history.

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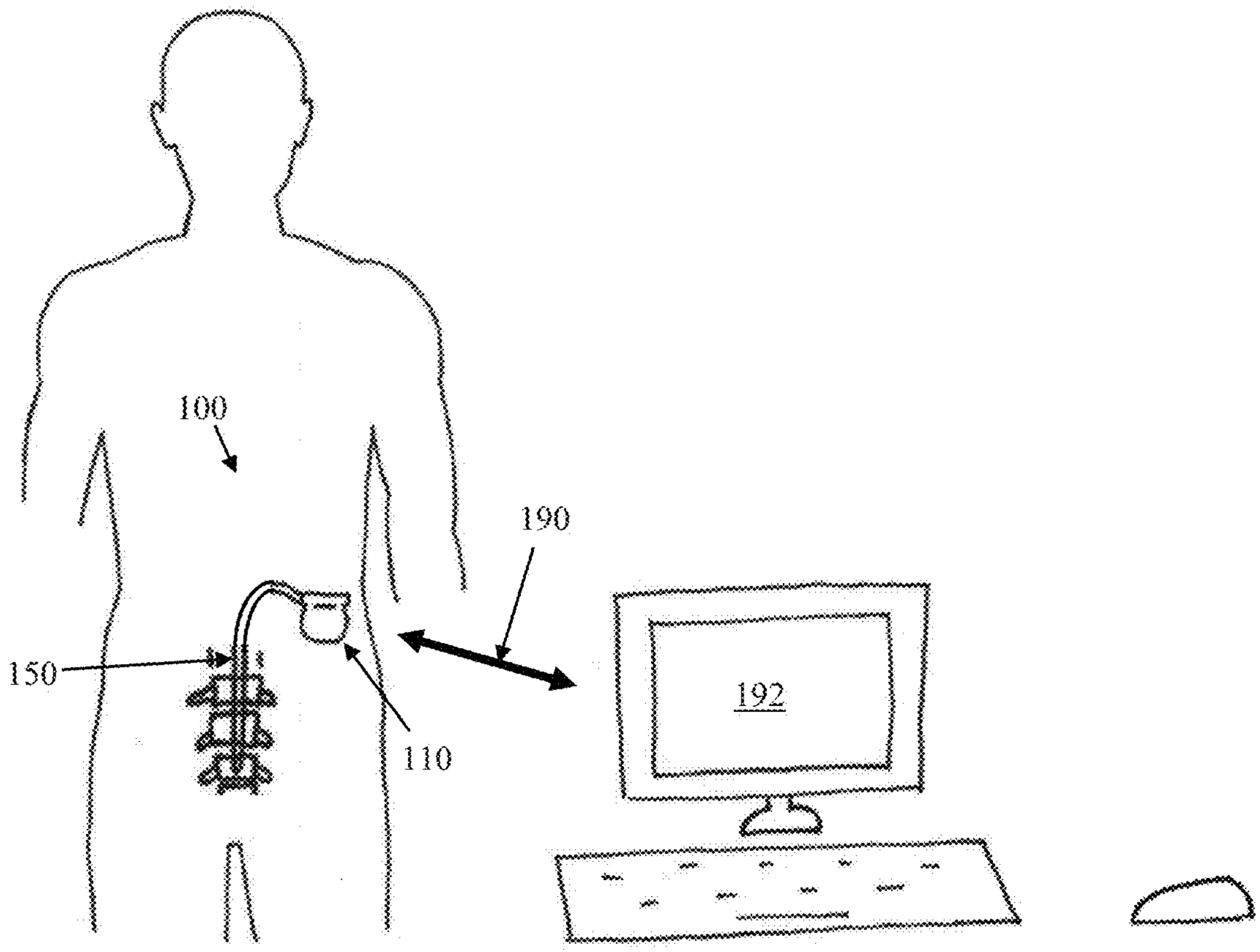
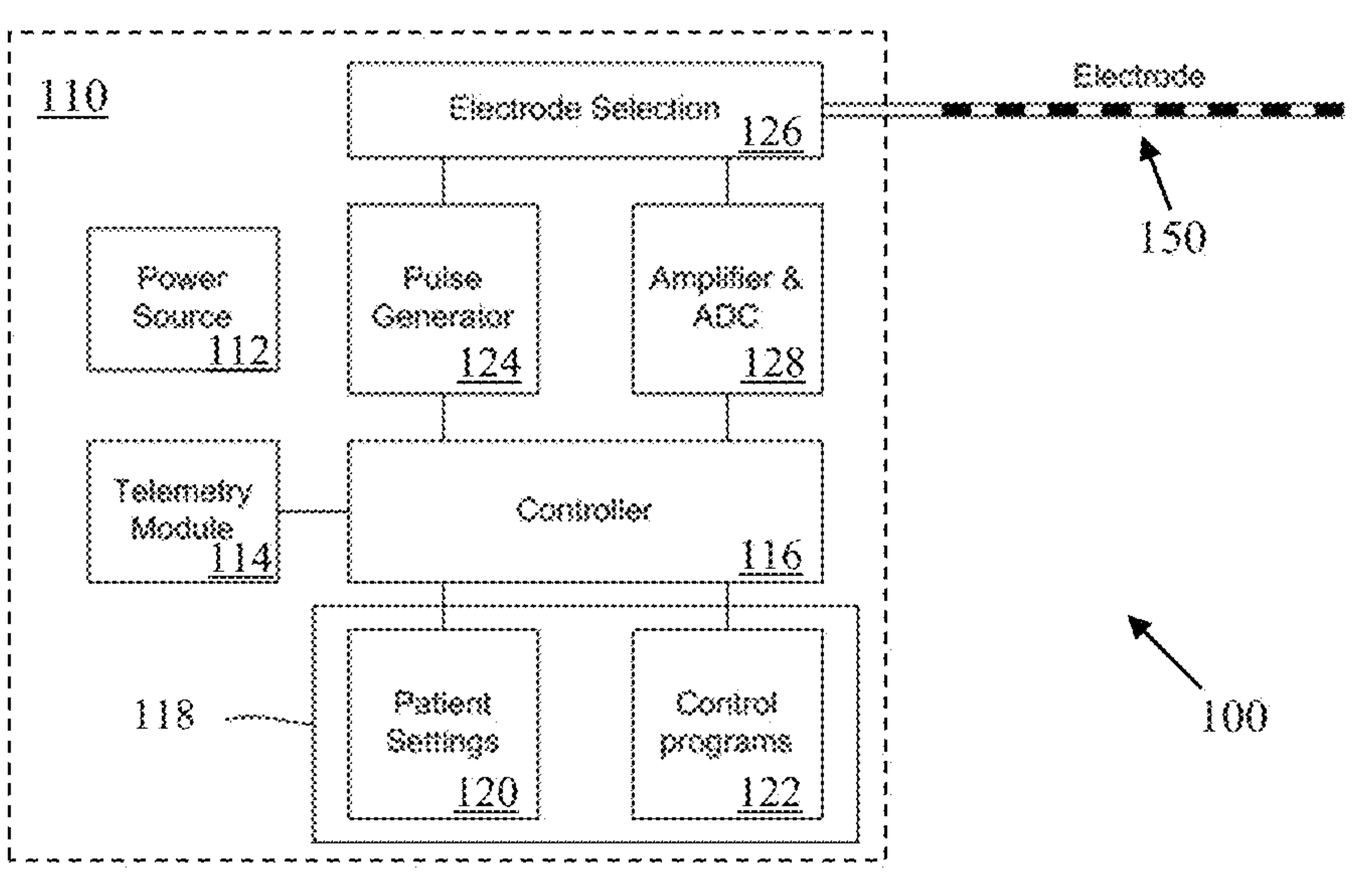



Figure 1

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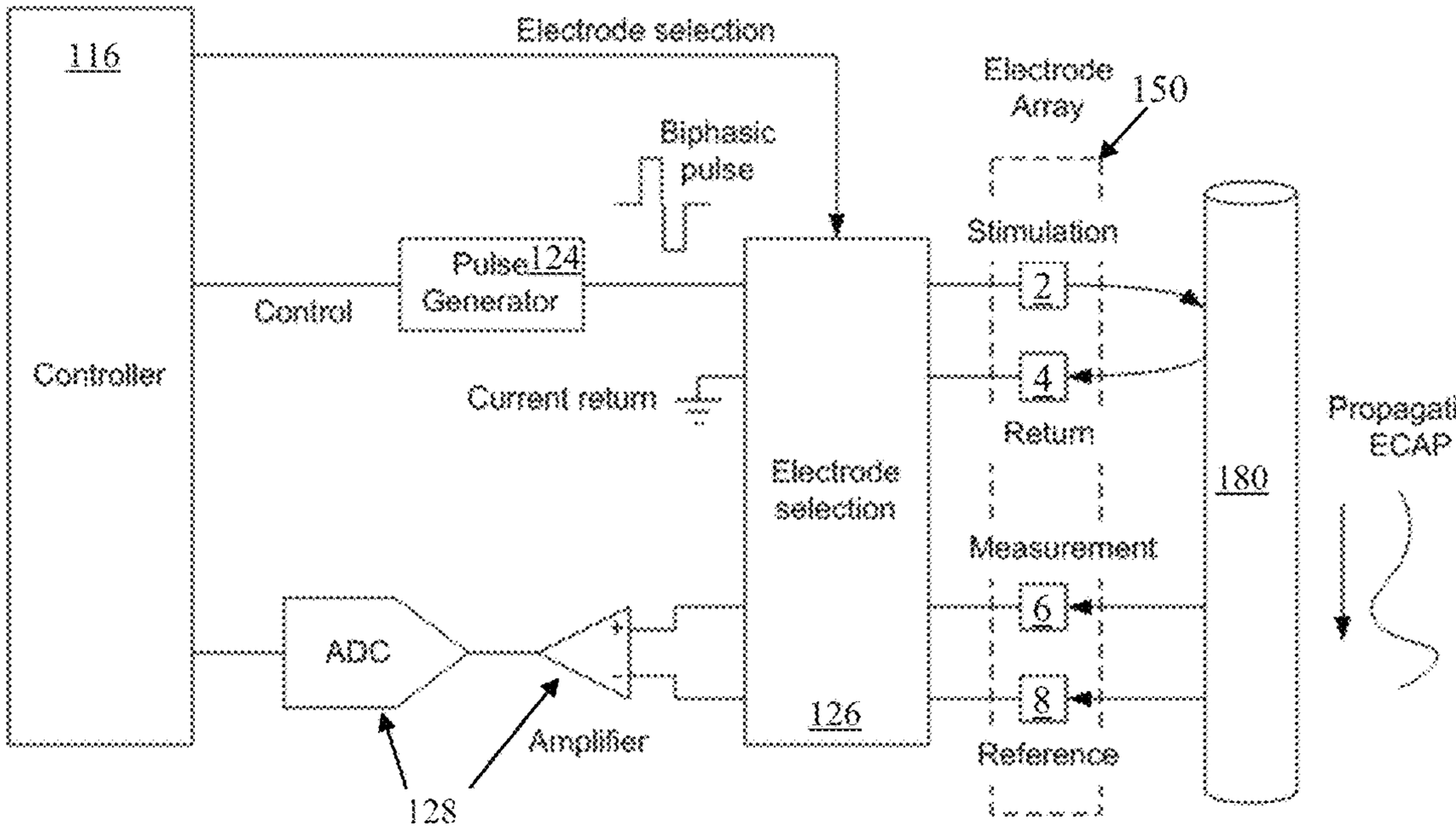



**Figure 3**

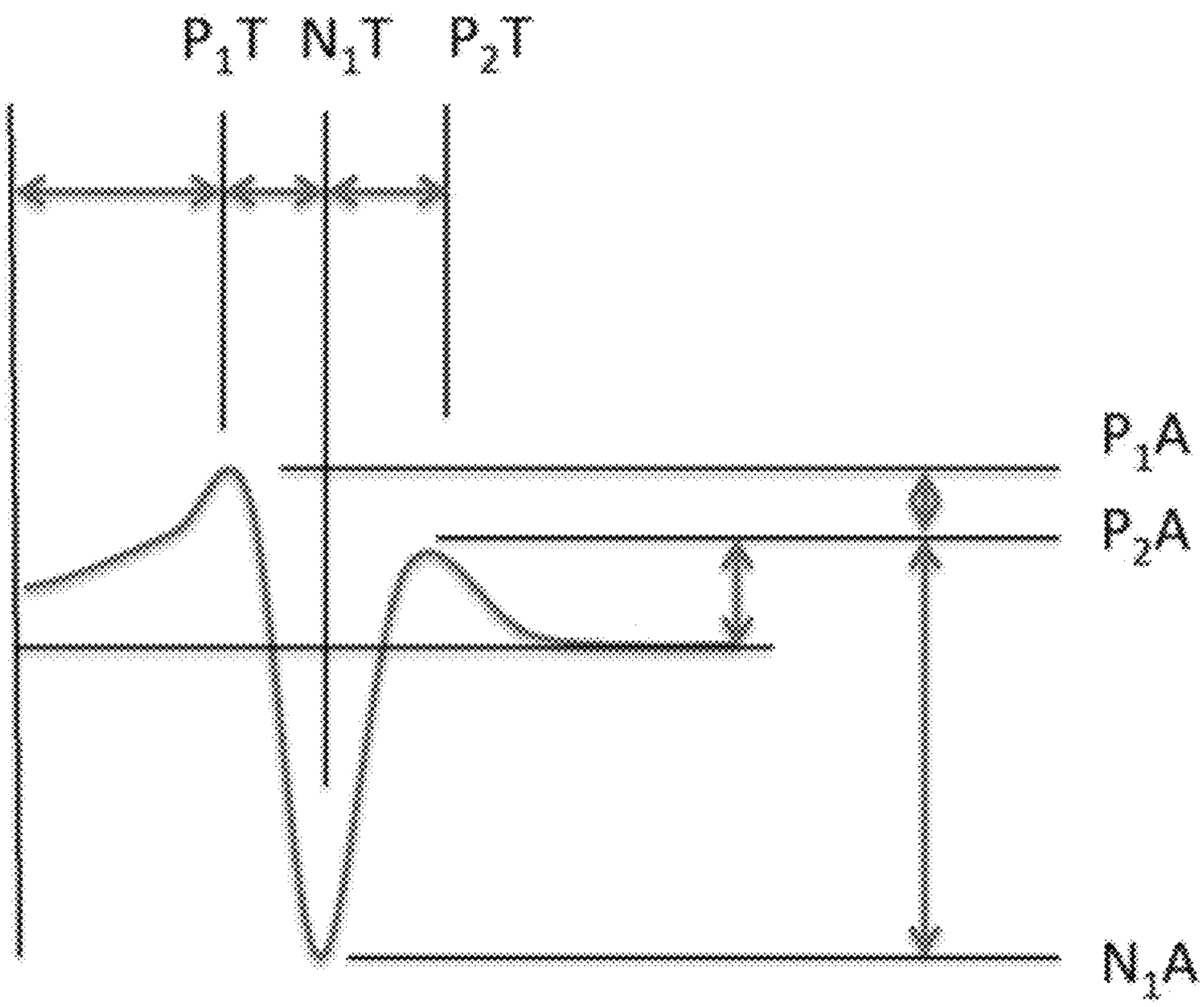
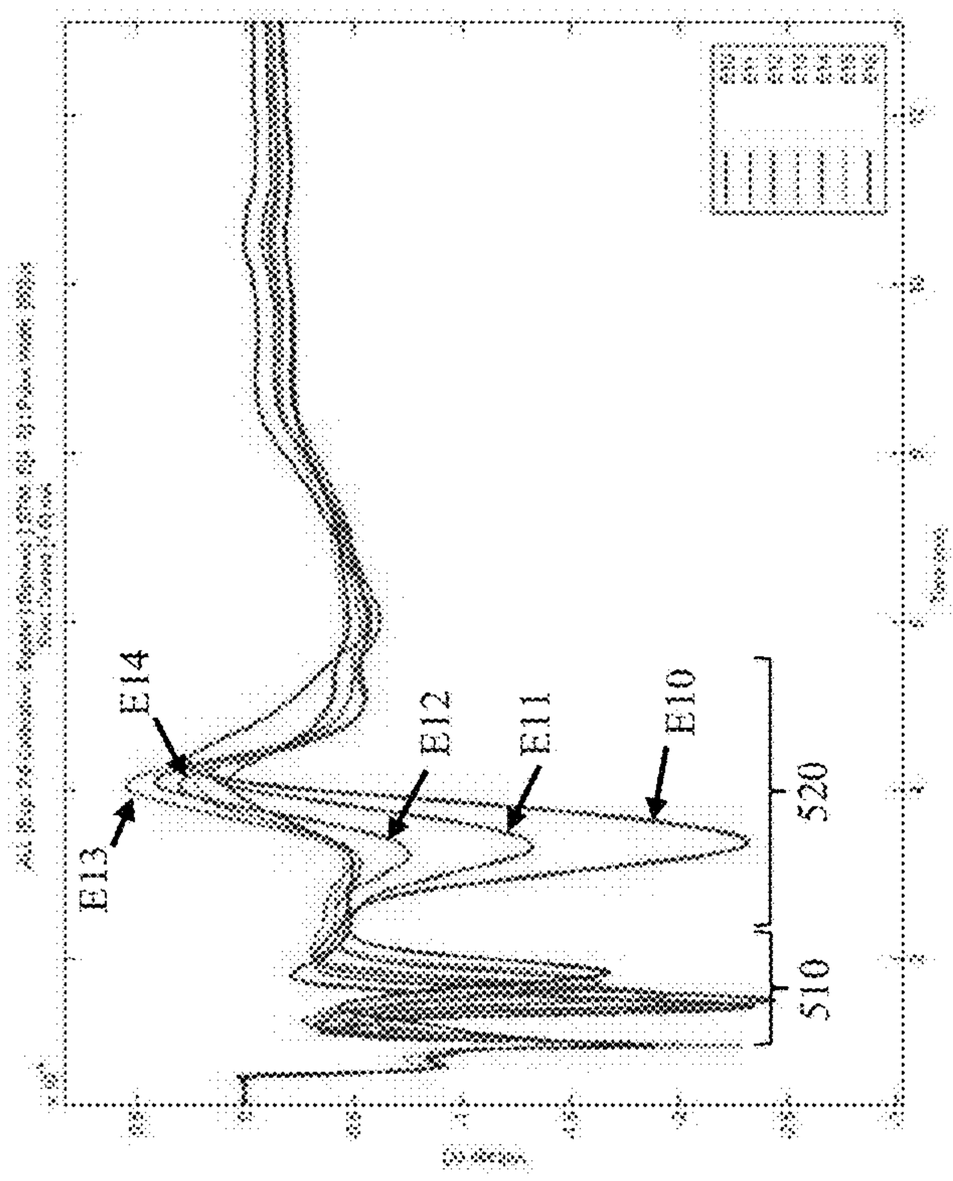
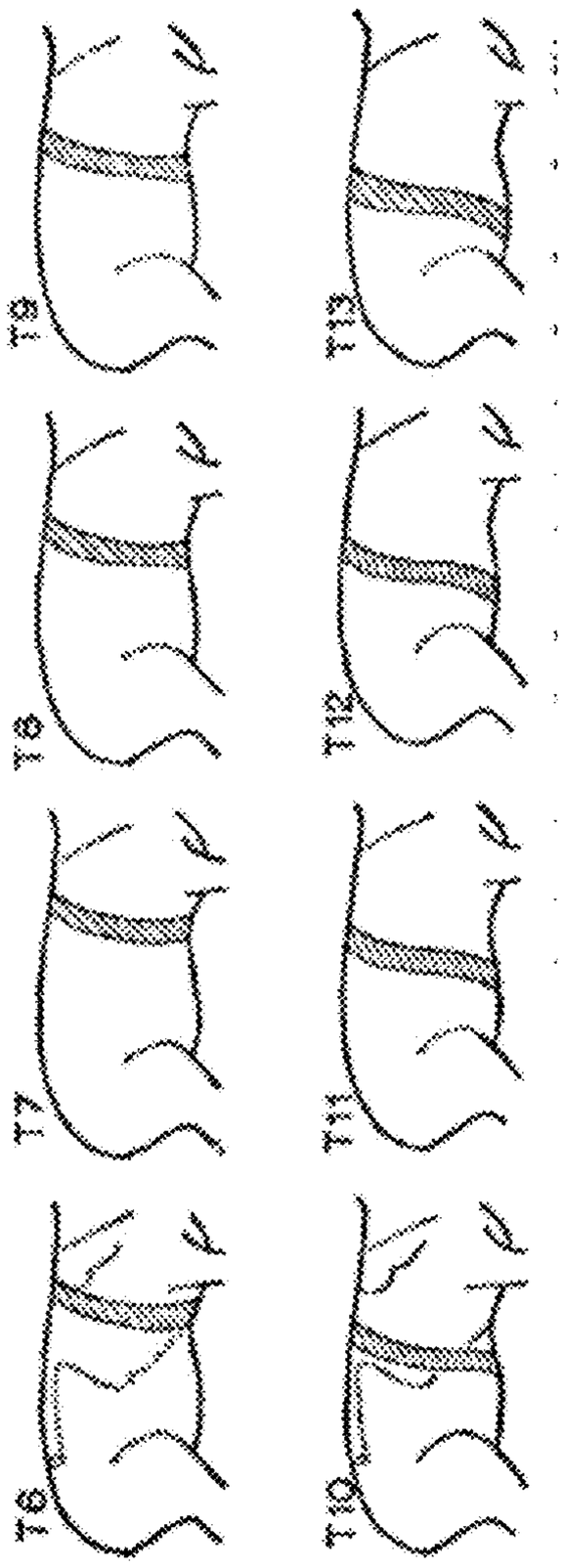
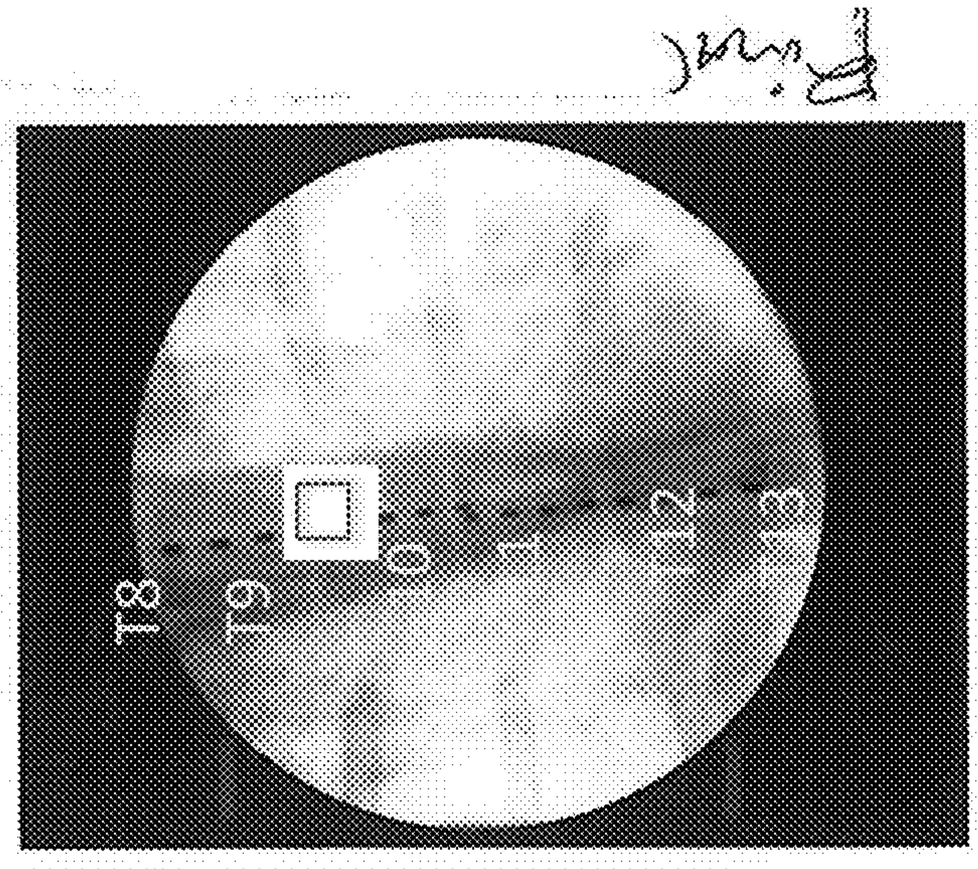



**Figure 4**



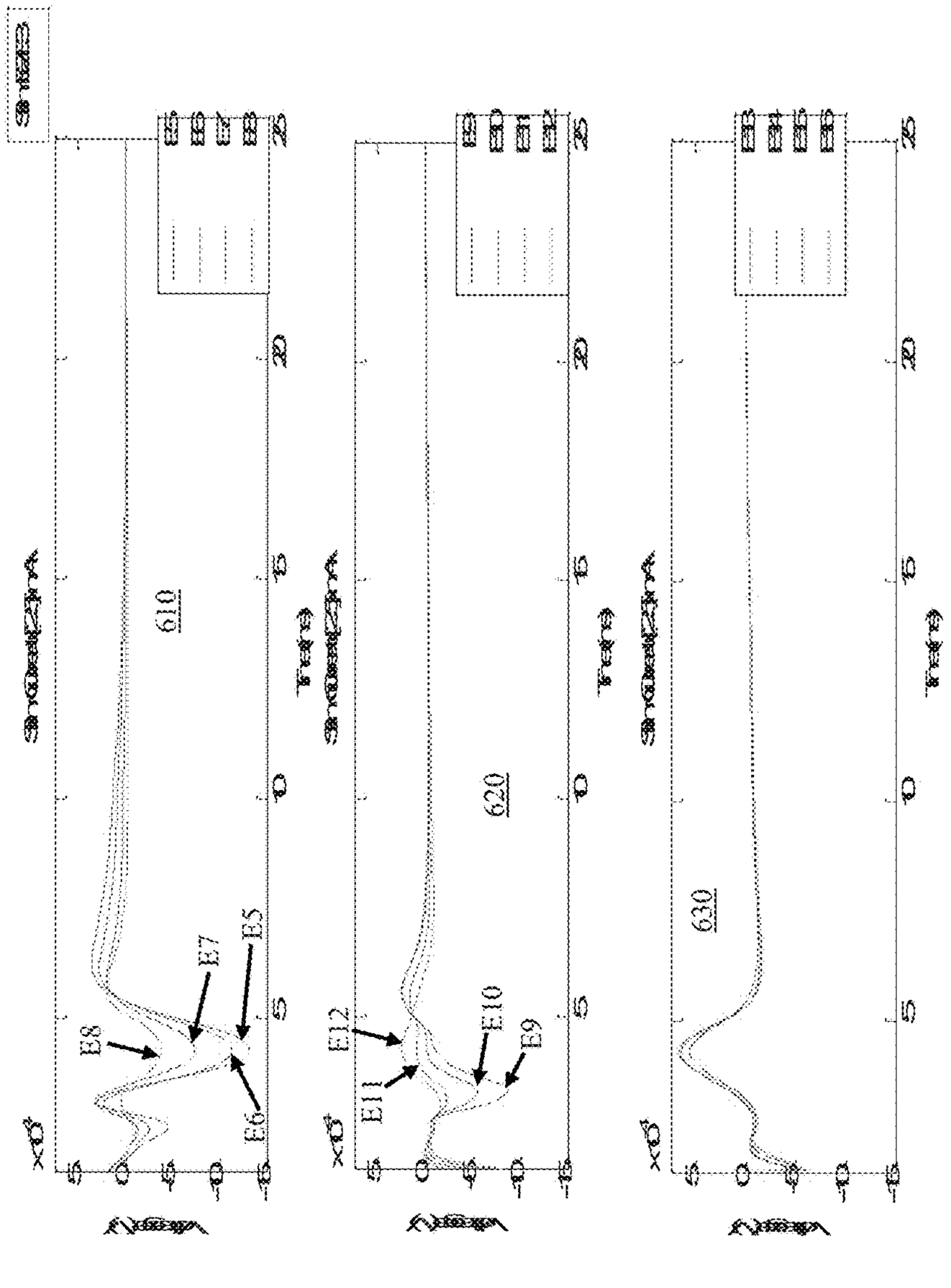



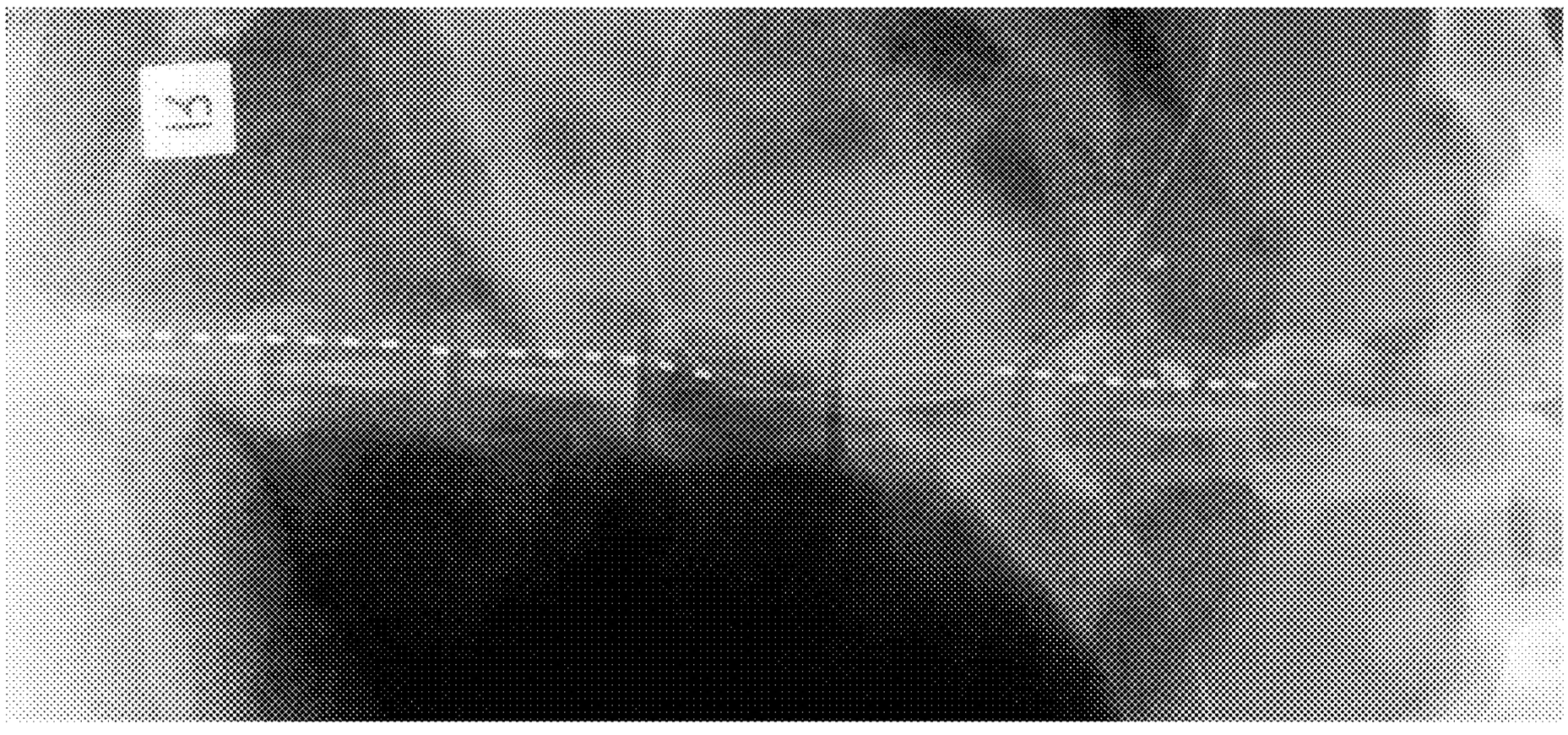




Sheep 7 top of T8 bottom T 13
The reference electrode was posterior

**Figure 5**

Figure 6



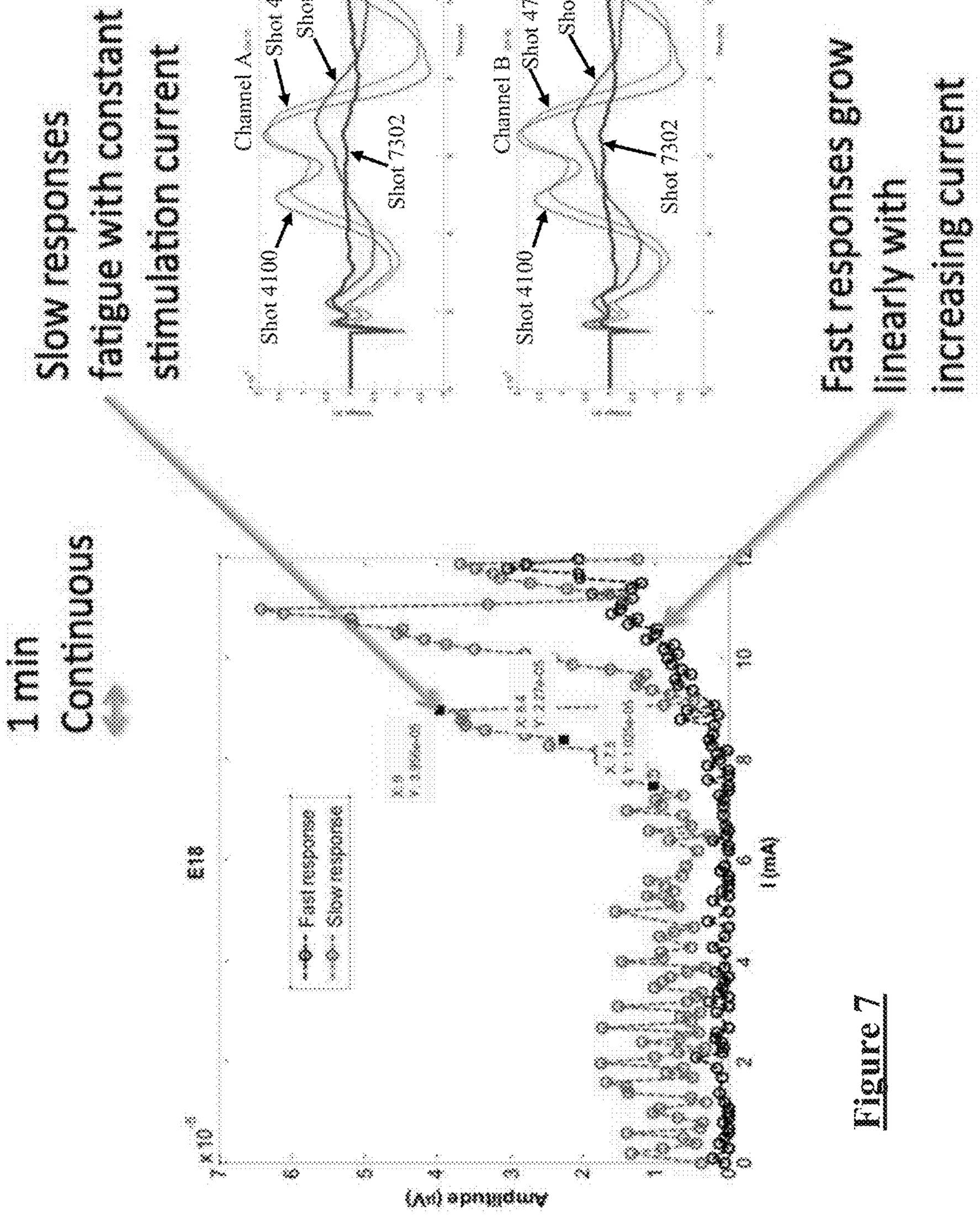

1 min
Continuous
Slow responses
fatigue with constant
stimulation current
Fast responses grow
linearly with
increasing current
Channel A
Channel B
Shot 4100
Shot 4732
Shot 5302
Shot 7302
Amplitude (μV)
I (mA)
Fast response
Slow response

Figure 7

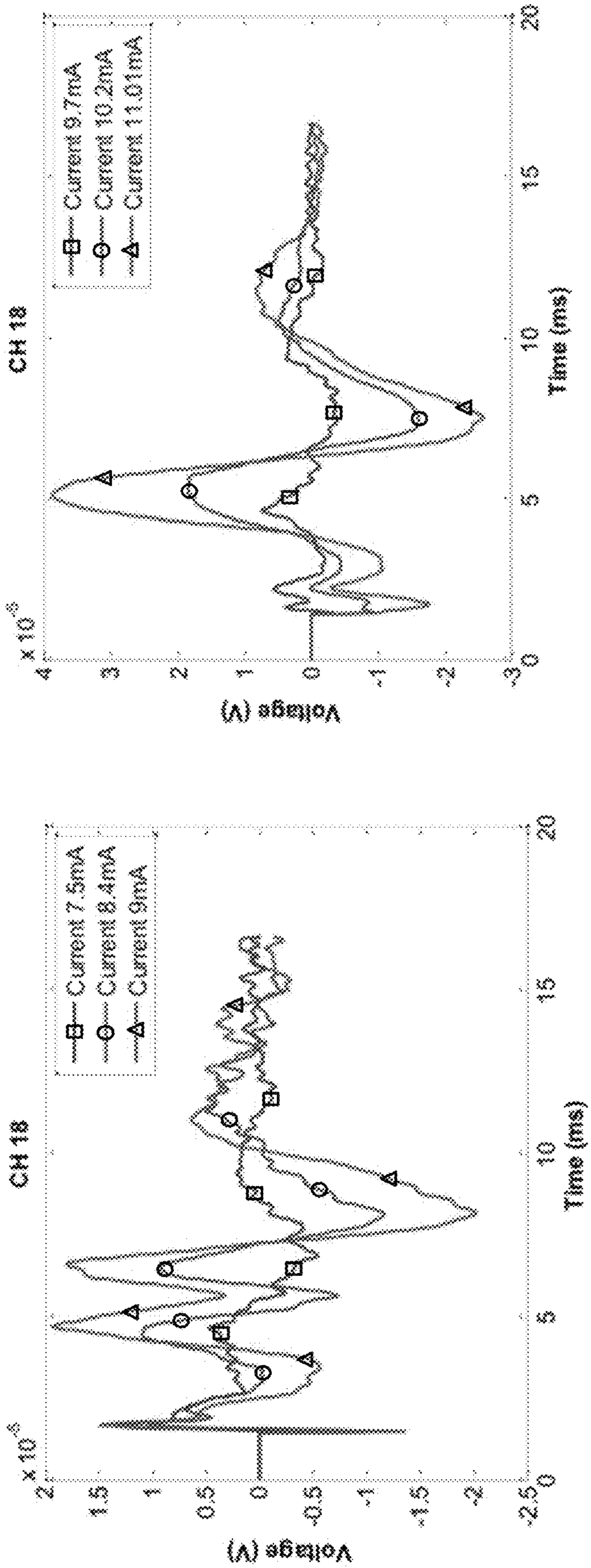

Current 9.7mA
Current 10.2mA
Current 11.01mA
CH 18
Voltage (V)
Time (ms)
Current 7.5mA
Current 8.4mA
Current 9mA
CH 18
Voltage (V)
Time (ms)

Figure 8

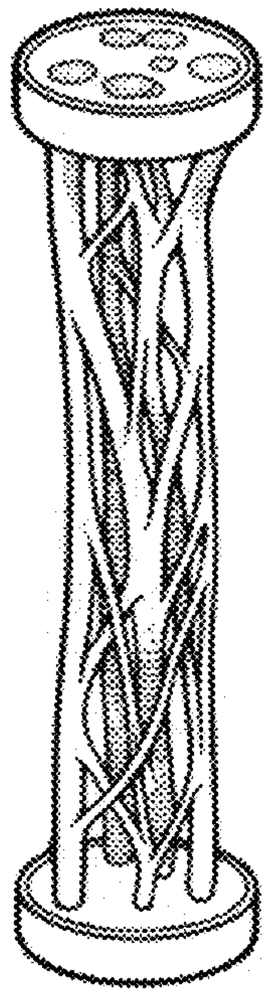


Figure 9

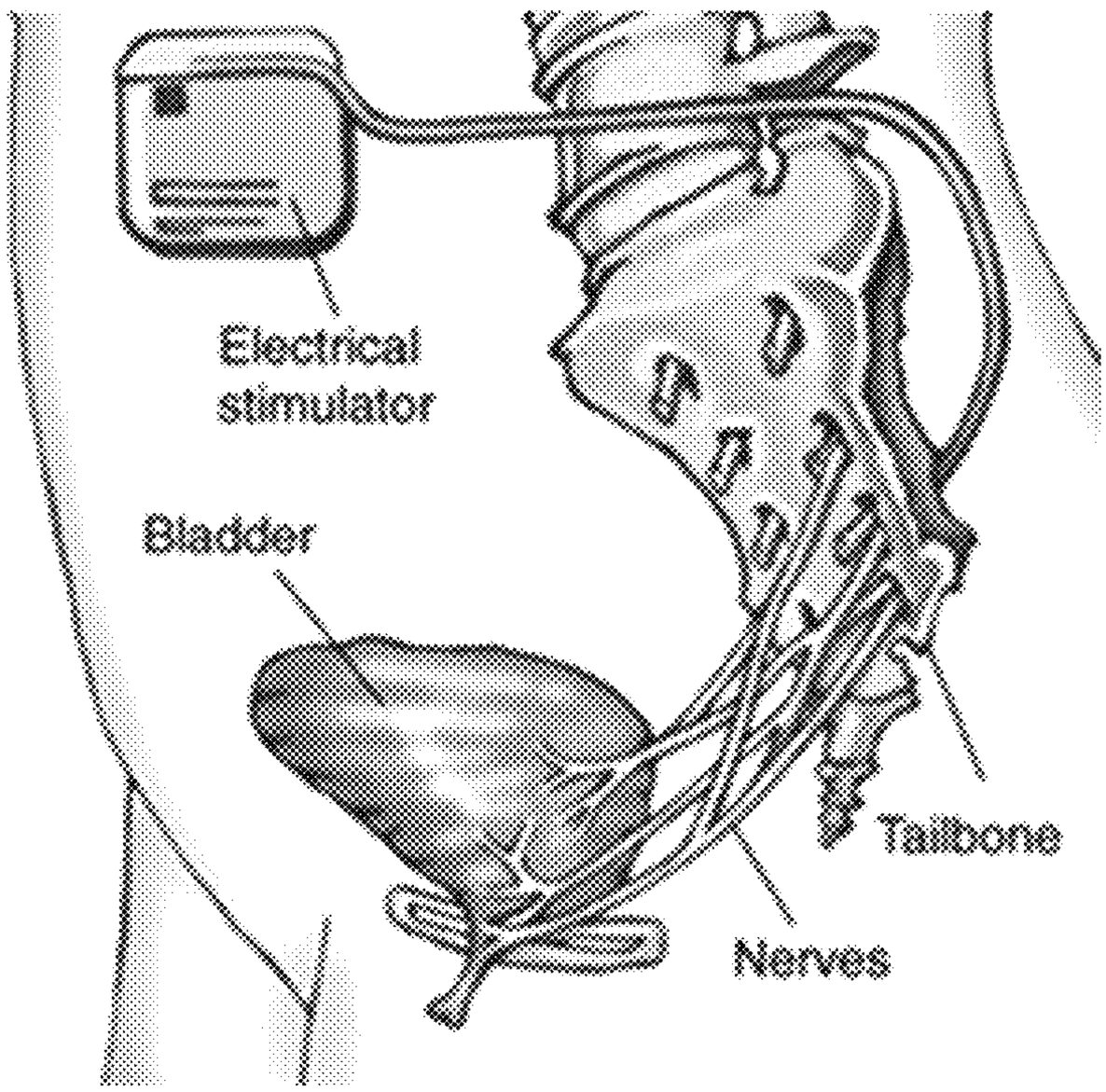



Figure 10

# MOTOR FIBRE NEUROMODULATION

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a national stage of Application No. PCT/AU2016/050439, filed Jun. 1, 2016, which application claims the benefit of Australian Provisional Patent Application No. 2015902393 filed Jun. 1, 2015, the disclosures of which are incorporated herein by reference in their entireties.

## TECHNICAL FIELD

The present invention relates to neuromodulation delivered to motor fibres, and in particular to a method and device for assessing motor fibre and muscle recruitment from neural response measurements.

## BACKGROUND OF THE INVENTION

There are a range of situations in which it is desirable to apply neural stimuli in order to give rise to a compound action potential (CAP). A neuromodulation system applies an electrical pulse to tissue in order to generate a therapeutic effect. Such a system typically comprises an implanted electrical pulse generator, and a power source such as a battery that may be rechargeable by transcutaneous inductive transfer. An electrode array is connected to the pulse generator, and is positioned adjacent the target neural pathway(s). An electrical pulse applied to the neural pathway by an electrode causes the depolarisation of neurons, and generation of propagating action potentials. In almost all neuromodulation applications, a single class of fibre response is desired, but the stimulus waveforms employed can recruit action potentials on other classes of fibres which cause unwanted side effects.

Another control problem, facing neuromodulation systems of all types, is achieving neural recruitment at a sufficient level required for therapeutic effect, but at minimal expenditure of energy. The power consumption of the stimulation paradigm has a direct effect on battery requirements which in turn affects the device's physical size and lifetime. For rechargeable systems, increased power consumption results in more frequent charging and, given that batteries only permit a limited number of charging cycles, ultimately this reduces the implanted lifetime of the device.

Neural modulation can be applied to activate a selected muscle group. One example of such neuromodulation is sacral nerve stimulation, in which stimulation frequencies are typically low (<20 Hz) and the currents are usually quite high (up to 7 mA). Without intending to be limited by theory, it is generally thought that sacral nerve stimulation induces a reflex inhibitory effect on the detrusor muscle of the urinary bladder through afferent and efferent fibers in the sacral nerves. Following implantation of a sacral nerve neuromodulator, adjusting the stimulus amplitude and frequency in current stimulation systems is a trial and error procedure. The stimulus amplitude is turned up until a motor response is recorded or the patient informs the programmer that paraesthesias are generated. The amplitude is then reduced below perception threshold and set to that level, but how much reduction is adequate to avoid undesirable motor responses or paraesthesias while still maintaining appropriate therapeutic effect is poorly known.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.



Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

In this specification, a statement that an element may be "at least one of" a list of options is to be understood that the element may be any one of the listed options, or may be any combination of two or more of the listed options.

## SUMMARY OF THE INVENTION

According to a first aspect the present invention provides a method of assessing a motor response to neural stimulation, the method comprising:

applying electrical stimuli from a first electrode to a selected neural pathway to evoke an efferent neural response;

measuring a slow neural response upon the neural pathway evoked by the electrical stimuli;

based on the slow neural response, assessing a motor response of at least one muscle to the stimuli.

According to a second aspect the present invention provides a neurostimulator device comprising:

at least one stimulus electrode configured to be positioned adjacent to a neural pathway and to apply electrical stimuli to the neural pathway to evoke an efferent neural response;

at least one sense electrode configured to be positioned adjacent to the neural pathway and to measure a slow neural response upon the neural pathway evoked by the electrical stimuli; and

a processor for assessing a motor response of at least one muscle to the stimuli, based on the slow neural response.

The present invention further provides computer software, or a computer program product comprising computer program code means, or a non-transitory computer readable medium, or a computing device operating under the control of said software or product, configured to apply electrical stimuli from a first electrode to a selected neural pathway to evoke an efferent neural response, further configured to measure a slow neural response upon the neural pathway evoked by the electrical stimuli, and further configured to assess a motor response of at least one muscle to the stimuli, based on the slow neural response.

Some embodiments of the invention may be applied intra-operatively, in order to use the observed slow response to locate the nerve and optimally position the electrode(s).

Some embodiments of the invention may further comprise applying stimuli at a first level for a period of time sufficient to fatigue a recruited portion of the associated muscle fibre population, and then applying stimuli at an increased level in order to recruit and assess a further portion of the muscle fibre population. Such embodiments may further comprise fatiguing the muscle fibres at various stimulus levels in order to explore characteristics of recruitment of each portion of the muscle fibre population.

Some embodiments may further comprise assessing a pattern or morphology of the slow response, to determine which muscle groups are being recruited by the stimulation.

Preferred embodiments further measure a fast neural response to the stimuli. The fast response may be defined as the neural response observed in a time period of 0-2 ms or 0-2.5 ms after a stimulus. The slow response may in some embodiments comprise the neural response observed during a time period of 2-15 ms after a stimulus, or 2.5-8 ms after a stimulus.

In some embodiments the stimulus is applied to preferentially evoke motor responses whether to stimulate motor activity or suppress motor activity. Thus it is to be appreciated that the motor response of the at least one muscle to the stimuli assessed by the present invention could comprise either or both of an increase in or commencement of a muscle response, or a reduction in or absence of a muscle response.

It is to be noted that a muscle fibre or group may be innervated by multiple nerves, and the "neural pathway" is defined herein to encompass such situations. In particular, in some embodiments the evoked efferent neural response may arise on one nerve innervating the muscle, while the late response may be observed on another nerve which is associated with the same muscle and which carries the or a late response returned from the muscle. For example, stimulation may be applied to a neural pathway on a first side of the body, and the late response may be observed upon a neural pathway on a contralateral second side of the body.

In some embodiments, the neural pathway comprises the sacral nerve. The muscle may comprise the detrusor muscle.

In some embodiments, the neural pathway is used for gastric pacing, and the muscle comprises a gastric muscle.

In some embodiments, the neural pathway is used for functional electrical stimulation (FES).

In some embodiments, the neural pathway is used for multifidus pacing, and the muscle comprises the multifidus.

## BRIEF DESCRIPTION OF THE DRAWINGS

An example of the invention will now be described with reference to the accompanying drawings, in which:

FIG. **1** schematically illustrates an implanted sacral nerve stimulator;

FIG. **2** is a block diagram of the implanted neurostimulator;

FIG. **3** is a schematic illustrating interaction of the implanted stimulator with a nerve;

FIG. **4** illustrates the typical form of an electrically evoked compound action potential (ECAP) of a healthy subject;

FIG. **5** shows fast and slow responses obtained from the sheep spinal cord;

FIG. **6** is a plot of fast responses and slow responses arising from stimulation;

FIG. **7** shows fatigue in the amplitude of slow responses;

FIG. **8** shows that slow responses have a different morphology in different portions of the muscle fibre population;

FIG. **9** illustrates nerve fascicle distribution in a nerve fibre bundle; and

FIG. **10** shows the anatomy of sacral nerve stimulation for bladder control.

## DESCRIPTION OF THE PREFERRED EMBODIMENTS

FIG. **1** schematically illustrates an implanted sacral nerve stimulator **100**. Stimulator **100** comprises an electronics module **110** implanted at a suitable location in the patient's lower abdominal area or posterior superior gluteal region, and an electrode assembly **150** implanted within the sacrum and connected to the module **110** by a suitable lead. Numerous aspects of operation of implanted neural device **100** are reconfigurable by an external control device **192**. Moreover, implanted neural device **100** serves a data gathering role, with gathered data being communicated to external device **192**.

FIG. **2** is a block diagram of the implanted neurostimulator **100**. Module **110** contains a battery **112** and a telemetry module **114**. In embodiments of the present invention, any suitable type of transcutaneous communication **190**, such as infrared (IR), electromagnetic, capacitive and inductive transfer, may be used by telemetry module **114** to transfer power and/or data between an external device **192** and the electronics module **110**.

Module controller **116** has an associated memory **118** storing patient settings **120**, control programs **122** and the like. Controller **116** controls a pulse generator **124** to generate stimuli in the form of current pulses in accordance with the patient settings **120** and control programs **122**. Electrode selection module **126** switches the generated pulses to the appropriate electrode(s) of electrode array **150**, for delivery of the current pulse to the tissue surrounding the selected electrode(s). Other electrode arrays may also be provided and may be similarly addressed by electrode selection module **126**, for example as in the case of FIGS. **5** and **6**, discussed further below. Measurement circuitry **128** is configured to capture measurements of neural responses sensed at sense electrode(s) of the electrode array as selected by electrode selection module **126**.

FIG. **3** is a schematic illustrating interaction of the implanted stimulator **100** with a nerve **180**, in this case the sacral nerve however alternative embodiments may be positioned adjacent any desired neural tissue including a peripheral nerve, visceral nerve, parasympathetic nerve or a brain structure. Electrode selection module **126** selects a stimulation electrode **2** of electrode array **150** to deliver an electrical current pulse to surrounding tissue including nerve **180**, and also selects a return electrode **4** of the array **150** for stimulus current recovery to maintain a zero net charge transfer.

Delivery of an appropriate stimulus to the nerve **180** evokes a neural response comprising a compound action potential which will propagate along the nerve **180** as illustrated, for therapeutic purposes which in the case of a sacral nerve stimulator might be to stimulate motor function of desired muscle fibres of the detrusor. To this end the stimulus electrodes are used to deliver stimuli at <20 Hz.

The device **100** is further configured to sense the existence and intensity of compound action potentials (CAPs) propagating along nerve **180**, whether such CAPs are evoked by the stimulus from electrodes **2** and **4**, or otherwise evoked. To this end, any electrodes of the array **150** may be selected by the electrode selection module **126** to serve as measurement electrode **6** and measurement reference electrode **8**. Signals sensed by the measurement electrodes **6** and **8** are passed to measurement circuitry **128**, which for example may operate in accordance with the teachings of International Patent Application Publication No. WO2012155183 by the present applicant, the content of which is incorporated herein by reference.

FIG. **4** illustrates the typical form of an electrically evoked compound action potential (ECAP) of a healthy subject. The shape and duration of the compound action potential shown in FIG. **4** is predictable because it is a result of the ion currents produced by the ensemble of axons generating action potentials in response to stimulation. The action potentials generated among a large number of fibres

sum to form a compound action potential (CAP). The CAP is the sum of responses from a large number of single fibre action potentials. The CAP recorded is the result of a large number of different fibres depolarising. The propagation velocity of the action potential on each fibre is determined largely by the diameter of that fibre. The CAP generated from the firing of a group of similar fibres is measured as a positive peak potential P**1**, then a negative peak N**1**, followed by a second positive peak P**2**. This is caused by the region of activation passing the recording electrode as the action potentials propagate along the individual fibres. An observed electrically evoked CAP signal will typically have a maximum amplitude in the range of microvolts and a duration of 2-3 ms.

The CAP profile takes a typical form and can be characterised by any suitable parameter(s) of which some are indicated in FIG. **4**. Depending on the polarity of recording, a normal recorded profile may take an inverse form to that shown in FIG. **4**, i.e. having two negative peaks N**1** and N**2**, and one positive peak P**1**.

The present embodiment recognises that neural responses measured on the sacral nerve **180** not only provide the information shown in FIG. **4**, but also at a later time reveal information about the evoked motor response. That is, ECAP recordings from the sacral nerve demonstrate both fast and slow responses. The fast responses are as shown in FIG. **4** and are the result of stimulation of large diameter Aβ fibres in the nerve bundle. The slower responses occur in the timeframe of about 2.5-7 ms after delivery of a stimulus and, without intending to be limited by theory, are thought to be due to the activation of a muscle group through either direct stimulation of the motor fibre or through activation of the spinal reflex arc. Slow responses are consistent with the theory above i.e. sacral neuromodulation activates a muscle presumably the detrusor. The present invention recognizes that it is further possible to determine which muscle groups are recruited from the pattern of the slow response.

To this end, slow responses have been measured experimentally from the sheep spinal cord and it has been noted that there are differences in the responses observed, depending on the origin of the response. FIG. **5** shows both fast **510** and slow **520** propagating neural responses from the sheep spinal cord. The Xray in FIG. **5** shows the position of the electrodes and the animal drawings show the dermatomes innervated by the fibres from each of those dermatomes.

FIG. **6** is a plot of ECAPs (fast responses) and slow responses, arising from stimulating at the top of the array. In this case three electrode leads were used to stimulate and measure. In the x-ray of FIG. **6**, the top two electrode leads are placed in the normal direction (inserted in the rostral direction) whereas the bottom electrode lead was place retrograde direction. The stimulus was at T**13** and so the bottom electrode lead measures responses posterior (caudally) of the dermatome being stimulated. This is observed in the recording as a reversal in the polarity of the responses **630** relative to recordings **610** and **620**. That is, the recordings obtained from electrodes E**13** to E**16** show a positive amplitude whereas the responses **610** and **620** from further up the cord show a negative response.

This demonstrates that the sign and shape of the slow response, being the peaks in the 3-5 ms range in FIG. **6**, can be used to identify the location of the muscle group which is responding to the stimulus. The signal can be analysed in a number of different ways in order to extract information about the strength and source of the activation.

It is highly desirable in all neuromodulation applications which seek to affect a muscle group to achieve specificity i.e. selection of the targeted group and only that group. In the case of sacral nerve stimulation this is, according to theory, the detrusor muscle. Note that even if current theory is incorrect then it would also apply to other muscle groups for instance pelvic floor.

The present embodiment further provides for identification of the appropriate muscle group, by increasing the amplitude of the stimulation current, analysing the slow response, and identifying the slow response pattern which results. In this context it is to be understood that the slow response allows an understanding of muscle fibre activation to be derived from the late response in the neural measurements, providing similar information to electromyography (EMG).

Another property which is exploited by the present embodiment in identification of appropriate muscle groups is the fact that repetitive muscle fibre stimulation results in the fatigue of the muscle and loss of the slow response signal. In this regard, FIG. **7** shows the amplitude of both slow responses and fast responses (left panel) and the responses for two non-stimulating channels on the right panel. In this experiment the amplitude was increased and then held at 9 mA for two minutes. The amplitude of the response drops to zero as can be seen in the right panel as the muscle fatigues during the two minute period. Thus, an individual muscle group can be brought to fatigue with repetitive stimulation at a fixed amplitude. If the amplitude of the stimuli (or "shots" in FIG. **7**) is further increased from this point then additional muscle fibres are recruited and even though responses from those that have fatigued are no longer observable new responses are evoked, as seen in FIG. **7** as the amplitude increases beyond the first fatigue point at 9 mA and the second fatigue point at 11 mA. In FIG. **8**, note that the slow responses have a different morphology indicating some of the fibres are originating from an alternative muscle group location.

Identification of slow response patterns associated with muscle group activation, by measuring neural responses at or near the site of stimulation, is a matter of stimulating with an increase in amplitude over time and waiting at each selected current until the muscle group recruited at this stimulus level has fatigued, prior to the next step in current. Stimulation place perception or other measures of muscle group activation could be correlated with the response. In the case of the detrusor muscle this could be easily detected and correlated by using a catheter measuring the bladder pressure, for example. The bladder tends to respond to neural stimulation initially with rapid contraction followed by slow, longer-lasting relaxation. As the rapid contraction would only occur when the stimulus had reached the appropriate level to activate the detrusor muscle, then the slow response response derived from the neural observations could be determined by measurement of pressure change with a catheter. In this way the target pattern of slow responses for that muscle group can be determined by comparing observed slow responses to the catheter pressure results.

The above described staircase technique for filtering the responses can be used to determine the responses from individual groups of muscles. The contribution from all the fibres can then be compared with the sum of the responses obtained as the amplitude of stimulation is increased.

This technique has utility for any neural structure including spinal nerve roots. A further refinement can be made when the structure of a nerve bundle is considered. The individual fascicles in a nerve bundle meander through the length of the bundle as shown in FIG. **9**, and so the

sensitivity of a particular fascicle to stimulation will change depending on the position along the length of the fibre. The technique described above could be used to determine the signature of the muscle group which is desired to be targeted and then the electrode and or position chosen to best recruit that fibre group.

The continuous measurement of the evoked response can be used as a feedback target in sacral nerve stimulation, whereby the stimulation should be set to achieve an absence of slow response or a small slow response after having fatigued the muscle. There are a number of ways to achieve this. The stimulation rate could be adjusted and a feedback algorithm used to control the inter stimulus interval such that a response is not generated. This is achieved by stimulating and measuring the response and if a slow response is present then shortening the time until the next stimuli. Over a much longer time scale, increments in the time between stimuli could be made so that the responses start to appear and this way the optimal stimulation rate is achieved. This process could be done at the time of programming or continuously in real time by the implant.

Referring to FIG. **10**, the position of the nerve may change during the course of the therapy in particular for bladder control the filling of the bladder, bowels or patient movement would move the nerve within the sacral foramen and hence the efficacy of the stimulation would be altered as the nerve moves with respect to the electrode.

The fast response **510** is produced by the Aβ fibres and doesn't fatigue with stimulation in the same manner as the response from muscle groups. The Aβ response **510** also varies with amplitude depending on the distance of the responding fibre from the electrode. Thus, stimulation current adjustment for optimal motor fibre recruitment could be made on the basis of the amplitude of the Aβ response to account for movement of the nerve.

This change in stimulation current could be used to determine the state of the bladder, full or empty and further modifications made to the stimulus to account for this.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not limiting or restrictive.

The invention claimed is:

**1**. A method of assessing a motor response to neural stimulation, the method comprising:

applying electrical stimuli from an electrode to a selected neural pathway to evoke an efferent neural response, the stimuli being configured to modulate motor activity;

measuring a slow neural response upon the neural pathway evoked by the electrical stimuli; and

based on the slow neural response, assessing a motor response of at least one muscle to the stimuli.

**2**. The method of claim **1**, when applied intra-operatively in order to use the measured slow response to locate the neural pathway and optimally position the electrode.

**3**. The method of claim **1**, further comprising applying stimuli at a first level for a period of time sufficient to fatigue a recruited portion of the associated muscle fibre population, and then applying stimuli at an increased level in order to recruit and assess a further portion of the muscle fibre population.

**4**. The method of claim **3** further comprising fatiguing the muscle fibres at various stimulus levels in order to explore characteristics of recruitment of each portion of the muscle fibre population.

**5**. The method of claim **1**, further comprising assessing a pattern or morphology of the slow response, to determine which muscle groups are being recruited by the stimulation.

**6**. The method of claim **1**, further comprising measuring a fast neural response to the stimuli, the fast response being the neural response observed in a time period of 0-2.5 ms after a stimulus.

**7**. The method of claim **1**, wherein the slow response comprises the neural response observed during a time period of 2-15 ms after a stimulus.

**8**. The method of claim **1**, wherein the stimulus is applied to preferentially evoke motor responses, to stimulate motor activity or suppress motor activity.

**9**. The method of claim **1** wherein the neural pathway comprises a sacral nerve.

**10**. The method of claim **1** wherein the neural pathway is used for gastric pacing.

**11**. The method of claim **1** wherein the neural pathway is used for functional electrical stimulation (FES).

**12**. The method of claim **1**, wherein the neural pathway is used for multifidus pacing.

**13**. A neurostimulator device comprising:

at least one stimulus electrode configured to be positioned adjacent to a neural pathway and to apply electrical stimuli to the neural pathway to evoke an efferent neural response, the stimuli being configured to modulate motor activity;

at least one sense electrode configured to be positioned adjacent to the neural pathway and to measure a slow neural response upon the neural pathway evoked by the electrical stimuli; and

a processor for assessing a motor response of at least one muscle to the stimuli, based on the slow neural response.

**14**. The neurostimulator device of claim **13**, configured to apply the electrical stimuli intra-operatively in order to use the measured slow response to locate the neural pathway and optimally position the electrode(s).

**15**. The neurostimulator device of claim **13**, wherein the processor is configured to further apply stimuli at a first level for a period of time sufficient to fatigue a recruited portion of muscle fibre population associated with the at least one muscle, and to then apply stimuli at an increased level in order to recruit and assess a further portion of the muscle fibre population.

**16**. The neurostimulator device of claim **15** wherein the processor is further configured to apply stimuli to fatigue the muscle fibre population at various stimulus levels in order to explore characteristics of recruitment of each portion of the muscle fibre population.

**17**. The neurostimulator device of claim **13**, wherein the processor is further configured to measure a fast neural response to the stimuli, the fast response being the neural response observed in a time period of 0-2.5 ms after a stimulus.

**18**. The neurostimulator device of claim **13**, wherein the slow response comprises the neural response observed during a time period of 2-15 ms after a stimulus.

**19**. The neurostimulator device of claim **13** wherein the processor is configured to apply a stimulus to preferentially evoke motor responses, to stimulate motor activity or suppress motor activity.

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